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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/890,989	12/14/2001	Peter David Davis	U 013589-7	1811

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EXAMINER	
YU, MISOOK	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 06/03/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/890,989	DAVIS, PETER DAVID	
	Examiner	Art Unit	
	MISOOK YU, Ph.D	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 March 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-8,10,13,14,21 and 24-50* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☒ Claim(s) *13,14 and 33-49* is/are allowed.

6)☒ Claim(s) *1, 2, 4-9, 10, 21, 24-32* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *03/28/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Continued Examination Under 37 CFR 1.114

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 3/23/2005 has been entered.

Claims 1, 2, 4-9, 10, 13, 14, 21, 24- 50 are pending and examined on merits.

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office Action.

This Office action contains new grounds of rejection.

Claim Objections, Withdrawn

Objection of claims 33 and 37 are objected to because of the following informalities: claim 33, line 2 says "ad administration", and claim 37, line 1 says "acc according". Appropriate correction is required.

Claim Rejections - 35 USC § 112, Withdrawn

The rejection of claims of record under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention is withdrawn in view of the amendment.

Claim Rejections - 35 USC § 102, Maintained

Claims **1** remains rejected, and claims **2**, and **10**, and the new claim **50**, are newly rejected under 35 U.S.C. 102(b) as being anticipated by Bonfoco et al (1995, Experimental Cell Research, vol. 218, pages 189-200).

The claim is interpreted as drawn to a pharmaceutical composition comprising a tubulin binding agent, an NO synthase inhibitor, and a pharmaceutically acceptable carrier.

Applicant argues that Bonfoco et al., do not show, suggest, or enable a pharmaceutical composition comprising a tubulin binding agent, an NO synthase inhibitor, and a pharmaceutically acceptable carrier. Bonfoco et al., teach away from the instantly claimed invention "by teaching the necessity of including rat cells in the cultured medium described therein. A pharmaceutical composition cannot comprise rat cells." With respect to new claim 50, applicant concludes that the new claim 50 is, *a fortiori*, free of art because the transitional phrase "consisting essentially of" preclude the composition of Bonofoco et al., which contain rat cells among other in the culture medium.

These arguments have been fully considered but found unpersuasive. Consulting the specification, especially at page 3 lines 8-23, which discloses "The vascular damaging agent and the nitric oxide synthase inhibitor can be administered by the same route or by different routes" and "Each component of the method, the vascular damaging agent and the nitric oxide synthase inhibitor may independently be administered in a form suitable for the intended route of administration and such forms may be prepared in a conventional manner using conventional excipients", the Office

broadly interprets the scope of the instantly claimed invention includes colchicines and NMMA prepared as stock solutions in PBS as taught by Bonfoco et al., at page 190 under MATERIALS AND METHODS, sub-heading "Materials". The specification as originally filed fairly suggests that instant pharmaceutical composition does not have to be mixed together in **a single vial** with a single pharmaceutical excipient.

Claim Rejections - 35 USC § 103

The rejection of claims 2, 4-8, 13,14, 21, 24, 25, 26, 27, 31, 33, 34, 35, 36, 37, 38, 39, 40, 43, 44, 45, 46, and 48 under 35 U.S.C. 103(a) as being unpatentable over Chaplin et al (1998, a copy provided with ISR, Seminars in Radiation Oncology, vol. 8, pages 151-163) is **withdrawn** or moot for the claims canceled by the last amendment. The withdrawal, of the rejection of record for those claims drawn to a composition that are still pending, is due to the new grounds of rejection below. The withdrawal of the claims the rejection of record for those claims drawn to a composition that are still pending, is due to applicant's persuasive arguments.

Claims 1, 2, 28, and 13 remain rejected under 35 U.S.C. **103(a)** as being unpatentable over Chaplin et al (1998, a copy provided with ISR, Seminars in Radiation Oncology, vol. 8, pages 151-163) in view of Ohsumi et al., J Med Chem. 1998 Jul 30;41(16):3022-32.

Claims 1, 2, 13, and 28 are interpreted as drawn to pharmaceutical comprising an NO synthase inhibitor and **(Z)-2-Methoxy-5-[2-(3,4,5-trimethoxyphenyl)vinyl]-phenylamine** and method of treating cancer using said pharmaceutical.

Chaplin et al teach that an NO synthase inhibitor and tubulin binding agents have been used in the art for treating cancer.

Chaplin et al do not teach (Z)-2-Methoxy-5-[2-(3,4,5-trimethoxyphenyl)vinyl]-phenylamine.

However, Ohsumi et al., teach that (Z)-2-Methoxy-5-[2-(3,4,5-trimethoxyphenyl)vinyl]-phenylamine (note page 3030) is an analog of combretastin A-4 that has been effective in treating cancers, and the analog is also expected to have a action similar to combretastin A-4 disclosed by Chaplin et al.

Therefore, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make and use (Z)-2-Methoxy-5-[2-(3,4,5-trimethoxyphenyl)vinyl]-phenylamine with reasonable expectation of success since Chaplin et al., along with Oshumi et al., teach how to make and use each elements in the claims.

Claims 2, 29, 30, 32 are rejected under 35 U.S.C. **103(a)** as being unpatentable over Chaplin et al (1998, a copy provided with ISR, Seminars in Radiation Oncology, vol. 8, pages 151-163) in view of WO 96/18617 (IDS, AO).

The claims are interpreted as drawn to pharmaceutical comprising an NO synthase inhibitor listed in the each of the claims in combination of a tubulin binding agent.

See what Chaplin et al teach below. Chaplin et al., do not list the specific NO synthase inhibitors recited in the instant claims 29, 30, and 32.

However, WO 96/18617 teach that e specific NO synthase inhibitors recited in the instant claims 29, 30, and 32 are well known in the art.

Since the instant specification does not disclose any new compound, it would have been obvious to one having ordinary skill in the art at the time the claimed invention was made to make and use, (note WO 96/18617 teach various specifically recited NO synthase inhibitors have been used in as an pharmaceutical for cancer or other disease treatment), combining two known compounds useful for cancer treatment is obvious.

The Following Are New Grounds of Rejection

Claim Rejections - 35 USC § 102

Claims 1, 2, 4-8, 21, 24, 25, 26, 27, and 31 are rejected 35 U.S.C. 102(b) as being anticipated by Chaplin et al., of record (1998, a copy provided with ISR, Seminars in Radiation Oncology, vol. 8, pages 151-163).

The claims are interpreted as drawn to a pharmaceutical composition comprising two genuses, i.e. a tubulin binding agent and an NO synthase inhibitor with the specific agents belong to the two genuses recited in the dependent claims.

Applicant does not argue that the art of record teaches the two components of the claimed pharmaceutical composition. As the prosecution history indicates, it is not disputed that Chaplin et al., disclose that compounds belong to the two genuses, i.e. a tubulin binding agent and an NO synthase inhibitor with the specific agents belong to the two genuses recited in the dependent claims.

As stated above, the specification, especially at page 3 lines 8-23, which discloses "The vascular damaging agent and the nitric oxide synthase inhibitor can be administered by the same route or by different routes" and "Each component of the method, the vascular damaging agent and the nitric oxide synthase inhibitor may independently be administered in a form suitable for the intended route of administration and such forms may be prepared in a conventional manner using conventional excipients". Therefore, the Office broadly interprets the scope of the instantly claimed invention includes the tubulin binding agent and an NO synthase inhibitor used in clinical settings. Since Chaplin et al., disclose that all of those tubulin binding agent and an NO synthase inhibitor in clinical setting, it is the Office position that those tubulin binding agent and an NO synthase inhibitors are in a pharmaceutically acceptable excipient inherently.

The main issue is whether the art of record discloses an amount sufficient to cause damage to

The preamble recitation of a pharmaceutical, and other intended uses, i.e. an amount sufficient to cause damage to neovasculature and others are merely suggestive of an intended use and is not given patentable weight for purposes of comparing the claims with the prior art. The claims read on the composition *per se*, which is a tubulin binding agent and an NO synthase inhibitor with the specific agents belong to the two genuses recited in the dependent claims.

Allowable Subject Matter

Claims 13, 14, and 33-49 are allowed.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to MISOOK YU, Ph.D whose telephone number is 571-272-0839. The examiner can normally be reached on 8 A.M. to 5:30 P.M., every other Friday off.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

MISOOK YU, Ph.D
Examiner
Art Unit 1642